**4164-01-P**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**[Docket No. FDA-2014-N-1721]**

# Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Investigational New Drug Application Regulations

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA, Agency, or we) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

**DATES:** Submit written comments (including recommendations) on the collection of information by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

**ADDRESSES:** To ensure that comments on the information collection are received, OMB recommends that written comments be submitted to https://www.reginfo.gov/public/do/PRAMain. Find this particular information collection by selecting "Currently under Review - Open for Public Comments" or by using the search function. The OMB control number for this information collection is 0910-0014. Also include the FDA docket number found in brackets in the heading of this document.

**FOR FURTHER INFORMATION CONTACT:** Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-5733, PRAStaff@fda.hhs.gov.

**SUPPLEMENTARY INFORMATION:** In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

## Investigational New Drug Application Regulations--21 CFR Part 312

OMB Control Number 0910-0014--Revision

This information collection supports implementation of provisions of section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and of the licensing provisions of the Public Health Service Act (42 U.S.C. 201 *et seq*.) that govern investigational new drugs and investigational new drug applications (INDs). Implementing regulations are found in part 312 (21 CFR part 312), and provide for the issuance of guidance documents (see § 312.145 (21 CFR 312.145)) to assist persons in complying with the applicable requirements. The information collection applies to all clinical investigations subject to section 505 of the FD&C Act and include the following types of INDs:

- An Investigator IND is submitted by a physician who both initiates and investigates, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug or an approved product for a new indication or in a new patient population.
- Emergency Use IND allows FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with § 312.23 or § 312.20 (21 CFR 312.23 or 312.20). It is also used for patients who do not meet the criteria of an existing study protocol or if an approved study protocol does not exist.
- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and FDA's review takes place.

There are two IND categories: commercial and research (non-commercial).

General IND requirements include submitting an initial application as well as amendments to that application; submitting reports on significant revisions of clinical investigation plans; submitting information to the clinical trials data bank (https://clinicaltrials.gov) established by the National Institutes of Health/National Library of

Medicine, including expanded information on certain clinical trials and information on the results of these clinical trials; and reporting information on a drug's safety or effectiveness. In addition, sponsors are required to provide to FDA an annual summary of the previous year's clinical experience. The regulations also include recordkeeping requirements regarding the disposition of drugs, records regarding individual case histories, and certain other documentation verifying clinical investigators' fulfillment of responsibilities.

Form FDA 1571 entitled "Investigational New Drug Application (IND)" and Form FDA 1572 entitled "Statement of Investigator," were developed to assist respondents with the information collection and provide for uniform reporting of required data elements. The information is required to be submitted electronically. Individuals who are interested in receiving printed forms may send an email request to the FDA Forms Manager at formsmanager@OC.FDA.GOV. Fees may apply. Sponsors (including sponsor-investigators) interested in filing or updating a research IND may use a new web-based interface developed for use by mobile device or desktop to help in completing Form FDA 1571. The web-based interface also allows respondents to electronically submit completed Form FDA 1571 and associated files. For more information regarding Forms FDA 1571 and 1572 visit https://www.fda.gov/news-events/expanded-access/how-complete-form-fda-1571-and-form-fda-1572.

Human drug, biological product, and device product submissions must be accompanied by Form FDA 3674, as discussed in the guidance document entitled "Form FDA 3674--Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions" (updated November 2017), available from our website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/form-fda-3674-certifications-accompany-drug-biological-product-and-device-applicationssubmissions. The guidance document provides procedural instruction on completing and submitting required information to FDA. As

communicated in the instructions, the certification must accompany the application or submission and be included at the time of submission to FDA.

Regulations in part 312, subpart B, specify content and format requirements for applications, amendments, annual reporting, and withdrawals, including content and format requirements for protocol and information amendments. The regulations also explain phases of an investigation and set forth principles of IND submissions.

Regulations in part 312, subpart C, describe administrative actions pertaining to respondents' requests for and responses to clinical holds, terminations, and inactive IND status determinations, as well as various types of meetings (for example, End-of-Phase 2 and Pre-new drug application (NDA) meetings).

Regulations in part 312, subpart D, set forth sponsor and investigator responsibilities, including general responsibilities; transfer of obligations to a contract research organization; recordkeeping and record retention controls; reporting responsibilities; and responsibility for disposition of unused supply of investigational drug. The regulations also provide for investigator controls including review of ongoing investigations; compliance with requirements regarding the protection of human subjects and institutional review board assurance; and disqualification of clinical investigators.

Regulations in part 312, subpart E, sets forth requirements applicable to drugs intended to treat life-threatening and severely debilitating illnesses. The regulations establish procedures to reflect that physicians and patients accept greater risk or side effects from products that treat life-threatening and severely debilitating illnesses than they would accept from products that treat less serious illnesses. The procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated.

Regulations in part 312, subpart F, include provisions pertaining to import and export requirements; foreign clinical studies not conducted under an IND; the disclosure of data and information in an IND; and the issuance of guidance documents. We are revising the

information collection to account for burden that may be associated with recommendations found in Agency guidance documents.

- The guidance document entitled "Oversight of Clinical Investigations" (August 2013) communicates risk-based monitoring strategies and recommends plans for investigational studies of medical products, including human drug and biological products, medical devices, and combinations thereof. The guidance document is intended to enhance human subject protection and the quality of clinical trial data by focusing sponsor oversight on the most important aspects of study conduct and reporting. The guidance also communicates that sponsors can use a variety of approaches to fulfill responsibilities for monitoring clinical investigator conduct and performance in IND studies, and provides a description of strategies for monitoring activities to reflect a modern, risk-based approach. The guidance document recommends that respondents develop a written comprehensive monitoring plan and describes monitoring approaches for respondents to consider (Guidance Section IV.D.).
- The guidance document entitled "Pharmacogenomic Data Submissions" (March 2005) provides recommendations intended to assist sponsors submitting or holding INDs, NDAs, or biologics license applications (BLAs) with submission requirements for relevant data regarding drug safety and effectiveness (including §§ 312.22, 312.23, 312.31, 312.33, 314.50, 314.81, 601.2, and 601.12 (21 CFR 312.22, 312.23, 312.31, 312.33, 314.50, 314.81, 601.2 and 601.12)). Because the regulations were developed before the advent of widespread animal or human genetic or gene expression testing, the regulations do not specifically address when such data must be submitted. The guidance document includes content and format recommendations regarding pharmacogenomic data submissions. Although we have not received any pharmacogenomic submissions since 2013, we assume an average of 50 hours for preparing and providing information to FDA as recommended in the guidance and estimate one submission annually.

- The guidance document entitled "Adaptive Designs for Clinical Trials of Drugs and Biologics" (December 2019) was developed to assist sponsors and applicants submitting INDs, NDAs, BLAs, or supplemental applications on the appropriate use of adaptive designs for clinical trials to provide evidence of the effectiveness and safety of a drug or biologic. The guidance document describes important principles for designing, conducting, and reporting the results from an adaptive clinical trial, and advises sponsors on the types of information to submit to facilitate FDA evaluation of clinical trials with adaptive designs, including Bayesian adaptive and complex trials that rely on computer simulations for their design. The guidance document also helps to fulfill FDA Commitment Goals under the Prescription Drug User Fee Act pertaining to the enhancement of regulatory decision tools.

The referenced guidance documents are available for download from our website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents and were issued consistent with § 312.145 to help respondents comply with requirements in part 312. In publishing the respective notices of availability for each guidance document, we included an analysis under the PRA and invited public comment on the associated information collection recommendations. In addition, all Agency guidance documents are issued in accordance with our Good Guidance Practice regulations in 21 CFR 10.115, which provide for public comment at any time.

Regulations in part 312, subpart G, provide for drugs for investigational use in laboratory research animals or in vitro tests.

In the *Federal Register* of November 24, 2021 (86 FR 67060), we published a 60-day notice requesting public comment on the proposed collection of information. Although we received two general comments, neither discussed the four information collection topics solicited in our 60-day notice or suggested that we revise our burden estimate.

We estimate the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden for Biologics[1]

| 21 CFR Section; Activity | No. of Respondents | No. of Responses per Respondent | Total Annual Responses | Average Burden per Response | Total Hours |
|---|---|---|---|---|---|
| Subpart A--General Provisions: §§ 312.1 through 312.10 | | | | | |
| § 312.2(e); requests for FDA advice on the applicability of part 312 to a planned clinical investigation | 454 | 1.528 | 694 | 24 | 16,656 |
| § 312.8; requests to charge for an investigational drug | 14 | 1.64 | 23 | 48 | 1,104 |
| § 312.10; waiver requests | 5 | 1 | 5 | 24 | 120 |
| Subtotal Subpart A Center for Biologics Evaluation and Research (CBER) | | | 722 | | 17,880 |
| Subpart B--Investigational New Drug Application (IND): §§ 312.20 through 312.38 (Including Forms FDA 1571, 1572, and 3674) | | | | | |
| § 312.23(a) through (f); IND content and format | 2,075 | 3.382 | 7,018 | 300 | 2,105,400 |
| § 312.30(a) through (e); protocol amendments | 1,781 | 4.6692 | 8,316 | 284 | 2,361,744 |
| § 312.31(b); information amendments | 169 | 2.48 | 419 | 100 | 41,900 |
| § 312.32(c) and (d); IND safety reports | 224 | 10.59 | 2,372 | 32 | 75,904 |
| § 312.33(a) through (f); IND annual reports | 971 | 2.2739 | 2,208 | 360 | 794,880 |
| § 312.38(b) and (c); notifications of withdrawal of an IND | 712 | 3.057 | 2,177 | 28 | 60,956 |
| Subtotal Subpart B CBER | | | 22,510 | | 5,440,784 |
| Subpart C--Administrative Actions: §§ 312.40 through 312.48 | | | | | |
| § 312.42; clinical holds and requests for modification | 154 | 1.65 | 254 | 284 | 72,136 |
| § 312.44(c) and (d); sponsor responses to FDA when IND is terminated | 86 | 1.22 | 105 | 16 | 1,680 |
| § 312.45(a) and (b); sponsor requests for or responses to an inactive status determination of an IND by FDA | 48 | 1.48 | 71 | 12 | 852 |
| § 312.47; meetings, including "End-of-Phase 2" meetings and "Pre-NDA" meetings | 157 | 1.80 | 283 | 160 | 45,280 |
| Subtotal Subpart C CBER | | | 713 | | 119,948 |
| Subpart D--Responsibilities of Sponsors and Investigators: §§ 312.50 through 312.70 | | | | | |
| § 312.53(c); investigator reports submitted to the sponsor, including Form FDA 1572, curriculum vitae, clinical protocol, and financial disclosure | 1,068 | 5.23 | 5,586 | 80 | 446,880 |
| § 312.54(a); sponsor submissions to FDA concerning investigations involving an exception from informed consent under § 50.24 | 4 | 4.25 | 17 | 48 | 816 |
| § 312.54(b); sponsor notifications to FDA and others concerning an institutional review board determination that it cannot approve research because it does not meet the criteria in the exception from informed consent in § 50.24(a) | 1 | 1 | 1 | 48 | 48 |
| § 312.55(a); number of investigator brochures submitted by the sponsor to each investigator | 473 | 2.224 | 1,052 | 48 | 50,496 |
| § 312.55(b); number of sponsor reports to investigators on new observations, especially adverse reactions and safe use | 243 | 4.95 | 1,203 | 48 | 57,744 |

| | | | | | |
|---|---|---|---|---|---|
| § 312.56(b), (c), and (d); review of ongoing investigations and associated notifications; sponsor notifications | 915 | 2.948 | 2,698 | 80 | 215,840 |
| § 312.58; inspection of records and reports by FDA | 7 | 1 | 7 | 8 | 56 |
| § 312.64; number of investigator reports to the sponsor, including progress reports, safety reports, final reports, and financial disclosure reports | 2,728 | 3.816 | 10,411 | 24 | 249,864 |
| § 312.70; disqualification of a clinical investigator by FDA | 5 | 1 | 5 | 40 | 200 |
| Subtotal Subpart D CBER | | | 20,980 | | 1,021,944 |
| Subpart F--Miscellaneous: §§ 312.110 through 312.145 | | | | | |
| § 312.110(b)(4) and (b)(5); number of written certifications and written statements submitted to FDA relating to the export of an investigational drug | 18 | 1 | 18 | 75 | 1,350 |
| § 312.120(b); number of submissions to FDA of "supporting information" related to the use of foreign clinical studies not conducted under an IND | 280 | 9.82 | 2,750 | 32 | 88,000 |
| § 312.120(c); number of waiver requests submitted to FDA related to the use of foreign clinical studies not conducted under an IND | 7 | 2.29 | 16 | 24 | 384 |
| § 312.130; number of requests for disclosable information in an IND and for investigations involving an exception from informed consent under § 50.24 | 350 | 1.342 | 470 | 8 | 3,760 |
| Subtotal Subpart F CBER | | | 3,254 | | 93,494 |
| Total | | | 48,179 | | 6,694,050 |

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 2.--Estimated Annual Recordkeeping Burden for Biologics[1]

| 21 CFR Section; Activity | No. of Recordkeepers | No. of Records per Recordkeeper | Total Annual Records | Average Burden per Recordkeeping | Total Hours |
|---|---|---|---|---|---|
| Subpart D--Responsibilities of Sponsors and Investigators: §§ 312.50 through 312.70 | | | | | |
| § 312.52(a); sponsor records for the transfer of obligations to a contract research organization | 94 | 2.26 | 212 | 2 | 424 |
| § 312.57; sponsor recordkeeping showing the receipt, shipment, or other disposition of the investigational drug, and any financial interest | 335 | 2.70 | 904 | 100 | 90,400 |
| § 312.62(a); investigator recordkeeping of the disposition of drugs | 453 | 1 | 453 | 40 | 18,120 |
| § 312.62(b); investigator recordkeeping of case histories of individuals | 453 | 1 | 453 | 40 | 18,120 |
| Subtotal Subpart D CBER | | | 2,022 | | 127,064 |
| Subpart G--Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests | | | | | |
| § 312.160(a)(3); records pertaining to the shipment of drugs for investigational use in laboratory research animals or in vitro tests | 111 | 1.40 | 155 | 0.5 (30 minutes) | 78 |
| § 312.160(c) shipper records of alternative disposition of unused drugs | 111 | 1.40 | 155 | 0.5 (30 minutes) | 78 |
| Subtotal Subpart G CBER | | | 310 | | 156 |
| Total | | | 2,332 | | 127,220 |

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 3.--Estimated Annual Reporting Burden for Human Drugs[1]

| 21 CFR Section; Activity | No. of Respondents | No. of Responses per Respondent | Total Annual Responses | Average Burden per Response | Total Hours |
|---|---|---|---|---|---|
| Subpart A--General Provisions | | | | | |
| § 312.2(e); requests for FDA advice on the applicability of part 312 to a planned clinical investigation | 419 | 1 | 419 | 24 | 10,056 |
| § 312.8; requests to charge for an investigational drug | 25 | 1.28 | 32 | 48 | 1,536 |
| § 312.10; requests to waive a requirement in part 312 | 68 | 1.5 | 102 | 24 | 2,448 |
| Subtotal Subpart A Center for Drug Evaluation and Research (CDER) | | | 553 | | 14,040 |
| Subpart B--Investigational New Drug Application (IND) | | | | | |
| § 312.23(a) through (f); IND content and format (including Forms FDA 1571 and 3674) | 4,886 | 1.4662 | 7,164 | 300 | 2,149,200 |
| § 312.30(a) through (e); protocol amendments | 11,847 | 3.2367 | 38,346 | 284.25 | 10,899,850 |
| § 312.31(b); information amendments | 8,094 | 3.30899 | 26,783 | 100 | 2,678,300 |
| § 312.32(c) and (d); IND safety reports | 892 | 15.848 | 14,137 | 32 | 452,384 |
| § 312.33(a) through (f); IND annual reports | 3,777 | 2.9097 | 10,990 | 360 | 3,956,400 |
| § 312.38(b) and (c); notifications of withdrawal of an IND | 1,549 | 1.834 | 2,841 | 28 | 79,548 |
| Subtotal Subpart B CDER | | | 100,261 | | 20,215,682 |
| Subpart C--Administrative Actions: §§ 312.40 through 312.48 | | | | | |
| § 312.42; clinical holds and requests for modifications | 181 | 1.28 | 232 | 284 | 65,888 |
| § 312.44(c) and (d); sponsor responses to FDA when IND is terminated | 1 | 1 | 1 | 16 | 16 |
| § 312.45(a) and (b); sponsor requests for or responses to an inactive status determination of an IND by FDA | 213 | 1.72 | 367 | 12 | 4,404 |
| § 312.47; meetings, including “End-of-Phase 2” meetings and “Pre-NDA” meetings | 174 | 2.885 | 502 | 160 | 80,320 |
| Subtotal Subpart C CDER | | | 1,102 | | 150,628 |
| Subpart D--Responsibilities of Sponsors and Investigators | | | | | |
| § 312.54(a); sponsor submissions to FDA concerning investigations involving an exception from informed consent under § 50.24 | 7 | 1.14 | 8 | 48 | 384 |
| § 312.54(b); sponsor notifications to FDA and others concerning an institutional review board determination that it cannot approve research because it does not meet the criteria in the exception from informed consent in § 50.24(a) | 2 | 1 | 2 | 48 | 96 |
| § 312.56; review of ongoing investigations and associated notifications | 4,570 | 5.4689 | 24,993 | 80 | 1,999,440 |
| § 312.58; inspection of records and reports by FDA | 73 | 1 | 73 | 8 | 584 |
| § 312.70; disqualification of a clinical investigator by FDA. | 5 | 1 | 5 | 40 | 200 |
| Subtotal Subpart D CDER | | | 25,081 | | 2,000,704 |
| Subpart F--Miscellaneous: §§ 312.110 through 312.145 | | | | | |
| § 312.110(b)(4) and (b)(5); written certifications and written statements | 8 | 22.375 | 179 | 75 | 13,425 |

| | | | | | |
|---|---|---|---|---|---|
| submitted to FDA relating to the export of an investigational drug | | | | | |
| § 312.120(b); submissions to FDA of "supporting information" related to the use of foreign clinical studies not conducted under an IND | 1,964 | 7.352 | 14,440 | 32 | 462,080 |
| § 312.120(c); waiver requests submitted to FDA related to the use of foreign clinical studies not conducted under an IND | 68 | 1.5 | 102 | 24 | 2,448 |
| § 312.130; requests for disclosable information in an IND and for investigations involving an exception from informed consent under § 50.24 | 3 | 1 | 3 | 8 | 24 |
| § 312.145; Guidance Documents: | | | | | |
| Oversight of Clinical Investigations (2013) | 88 | 1.5 | 132 | 4 | 528 |
| Pharmacogenomic Data Submissions (2005) | 1 | 1 | 1 | 50 | 50 |
| Adaptive Designs for Clinical Trials of Drugs and Biologics (2019) | 55 | 4.727 | 260 | 50 | 13,000 |
| Subtotal Subpart F CDER | | | 15,117 | | 491,555 |
| Total | | | 142,114 | | 22,872,609 |

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 4.--Estimated Annual Recordkeeping Burden for Human Drugs[1]

| 21 CFR Section; Activity | No. of Recordkeepers | No. of Records per Recordkeeper | Total Annual Records | Average Burden per Recordkeeping | Total Hours |
|---|---|---|---|---|---|
| Subpart D--Responsibilities of Sponsors and Investigators | | | | | |
| § 312.52(a); transfer of obligations to a contract research organization | 466 | 3.107 | 1,448 | 300 | 434,400 |
| § 312.57; records showing the receipt, shipment, or other disposition of the investigational drug and any financial interests | 13,000 | 1 | 13,000 | 100 | 1,300,000 |
| § 312.62(a); records on disposition of drugs | 13,000 | 1 | 13,000 | 40 | 520,000 |
| § 312.62(b); records on case histories of individuals | 2,192 | 6.587 | 14,439 | 40 | 577,560 |
| Subtotal Subpart D CDER | | | 41,887 | | 2,831,960 |
| Subpart G--Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests | | | | | |
| § 312.160(a)(3); records pertaining to the shipment of drugs for investigational use in laboratory research animals or in vitro tests | 547 | 1.43 | 782 | 0.50 (30 minutes) | 391 |
| § 312.160(c); shipper records of alternative disposition of unused drugs | 547 | 1.43 | 782 | 0.50 (30 minutes) | 391 |
| Subtotal | | | 1,564 | | 782 |
| Total | | | 43,451 | | 2,832,742 |

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

The information collection reflects program changes and adjustments. We have revised the information collection to account for burden that may be incurred by respondents who choose to adopt or implement recommendations discussed in referenced Agency guidance documents intended to assist respondents in complying with regulatory requirements in part 312. We have also made adjustments to individual collection elements, specifically with regard to protocol amendments and emergency INDs for both human drugs and biological drugs. We attribute the

increase for these elements to a corresponding increase in submissions since last OMB review and approval of the information collection and the ongoing public health emergency. Finally, we have removed burden we attribute to provisions in part 312, subpart I: Expanded Access to Investigational Drugs for Treatment Use and are revising OMB control number 0910-0814 to include burden associated with information collection applicable to these regulatory provisions for efficiency of Agency operations. As a result of these cumulative changes and adjustments, the information collection reflects an overall decrease in both annual responses and burden hours.

Dated: February 10, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2022-03432 Filed: 2/16/2022 8:45 am; Publication Date: 2/17/2022]